UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA – WESTERN DIVISION

NEUROGRAFIX, a California corporation; WASHINGTON RESEARCH FOUNDATION, a not-for-profit Washington corporation, Plaintiffs, vs. SIEMENS MEDICAL SOLUTIONS USA, INC., a Delaware corporation; and SIEMENS AKTIENGESELLSCHAFT, a German corporation, Defendants.	Case No. 10-CV-1990 MRP (RZx) [Assigned to The Honorable Mariana R. Pfaelzer] **EXPERT REPORT OF DR. R. NICK BRYAN CONCERNING THE TERM "CONSPICUITY" IN U.S. PATENT NO. 5,560,360**
SIEMENS MEDICAL SOLUTIONS USA, INC., Counterclaimant, vs. NEUROGRAFIX, and WASHINGTON RESEARCH FOUNDATION Counterdefendants.	

EXPERT REPORT OF DR. R. NICK BRYAN
CONCERNING THE TERM "CONSPICUITY" IN U.S. PATENT NO. 5,560,360

1. I have been asked to render an opinion regarding the claim phrases "a conspicuity of the nerve that is at least 1.1 times that of the non-neural tissue" (as used or incorporated into claims 1 through 17) and "a conspicuity of the nerve that is at least 1.1 times that of any adjacent non-neural tissue" (as used or incorporated into claims 18 through 35) in the claims of U.S. Patent No. 5,560,360 ("the '360 patent"), and if called upon to testify, intend to testify to the opinions disclosed herein.

2. This report reflects conclusions that I have formed through my independent evaluation and analysis. If called upon to testify in this matter, I anticipate that my testimony will concern the matters addressed in this report, the attachments to the report, and the materials I relied upon in developing my opinions, as well as any background information concerning the technology areas at issue and my own education and experience in those areas.

3. This report is based on my analysis to date, and sets forth my opinions about certain claims, and particularly certain phrases used in the claims, of the '360 patent. I reserve the right to respond to any rebuttal that Plaintiffs offer in response to these opinions. I also reserve the right to supplement my opinions if Plaintiffs change their proposed claim constructions, or upon the discovery or production of additional information. I also reserve the right to supplement my opinions in the event the Court modifies or supplements its claim construction.

I. Background and Qualifications

4. I am the Eugene P. Pendergrass Professor of Radiology and Chair of the Department of Radiology at the University of Pennsylvania. I received an M.D. from the University of Texas in 1969, and a PhD in Anatomy from the University of Texas in 1973. I have been the Chair of the Department of Radiology at the University of Pennsylvania since 1999. Before that, I was the Director of Diagnostic Radiology and Associate Director,

Radiologic and Imaging Sciences Program, at the Warren Grant Magnuson Clinical Center, National Institutes of Health ("NIH"), Bethesda, Maryland. From 1988-1997, I held a number of positions at the John Hopkins University School of Medicine, including the Vice Chairman for the Department of Radiology and the Director of the Neuroradiology Division.

5. I am a board certified radiologist with a subspecialty in neuroradiology. After receiving my M.D., I received training and experience in a number of positions related to radiology and neuroradiology, through a four-year combined internship, residency, and fellowship focusing on radiology/neuroradiology. This included a Fellowship in neuroanatomy for NIH and being an NIH Special Fellow in neuroradiology for the Neurological Institute of New York. I hold the following certificates for radiology and neuroradiology: American Board of Radiology, 1973; Diagnostic Radiology (Neuroradiology, 1995), 1974; American Board of Radiology Certification of Added Qualifications (CAQ) (Neuroradiology, 1995); American Board of Radiology (MOC) (Neuroradiology, 2004). Presently, I hold several teaching positions focusing on neuroradiology and neuroimaging, including courses for residents and fellow training. I am also a Fulbright Senior Scholar and have received Gold Medals from the American Society of Neuroradiology ("ASNR") and the Radiological Society of North America ("RSNA"). I am a Fellow of the American College of Radiology, and was on the Board of Chancellors from 2002-2009 for the same. I am also a Fellow of the International Society of Magnetic Resonance in Medicine ("ISMRM") and have sat on its Board of Trustees.

6. In addition, I have been the President of several international and national societies specializing in radiology and neuroradiology, including the Radiological Society of North America, the American Society of Head & Neck Radiology, and the American Society of

Neuroradiology. From 1999-2000, I was the Chairman of the Board for the Radiological Society of North America.

7. I actively research and study a variety of topics related to MRI design, radiology, and neuroradiology, including: cerebral MRI findings and cognitive functioning; applications of perfusion MRI for neurological studies; development of spatially-oriented databases for digital brain images; nuclear magnetic resonance evaluation of stroke; physiologic imaging of human brain tumors. I am also on the editorial board of numerous scientific publications, including, Academic Radiology, Radiology, Science Translational Medicine, and am a Consultant to the Editor of the Journal of Magnetic Resonance Imaging. I have published approximately 190 peer-reviewed scientific papers on various topics. My complete CV is attached as **Exhibit A**. I am being compensated $300 per hour.

II. Materials Considered

8. In reaching the opinions herein, I have considered: the ’360 patent; the prosecution history of the ’360 patent; the parties’ claim construction briefing and exhibits; Dr. Filler’s February 1, 2011 Rebuttal Expert Report (“Filler Rebuttal Report”) and exhibits; the DICOM data files of the images in the Filler Rebuttal Report; Dr. Moseley’s January 24, 2011 Opening Expert Report (“Moseley Opening Report”) and exhibits; and the Court’s claim construction order. I have also considered the February 9, 2011 deposition transcript of Dr. Michael Moseley, and the February 22, 2011 deposition transcript of Dr. Aaron Filler. I have also considered the documents, images, and software cited and/or discussed in this report or in the exhibits to this report. A complete list of my materials considered is attached as **Exhibit B**. In reaching my opinions, I have applied my experience in radiology, neuroradiology, and magnetic resonance, including my experience in tissue contrast mechanisms and image processing and analysis.

III. Legal Standards

A. Claim Indefiniteness Under 35 U.S.C. § 112, ¶ 2

9. I understand that a patent specification must conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his or her invention. 35 U.S.C. § 112, ¶ 2. I also understand that claims are indefinite if they do not reasonably apprise those skilled in the relevant art of the patent applicant's intended scope of the invention when read in light of the specification. I understand that claims are indefinite if they are insolubly ambiguous.

B. Level of Ordinary Skill in the Art

10. When interpreting a patent, including when determining whether the claims meet the definiteness requirement of 35 U.S.C. § 112, ¶ 2, I understand that such interpretation is viewed from the level of ordinary skill in that art at the time of the invention.

11. I understand that Plaintiffs contend that a person having ordinary skill in the art for the '360 patent is a medical doctor with an M.D., three years of residency and a 1 year fellowship in neuroradiology or musculoskeletal radiology and at least 2 years experience in neuroradiology or musculoskeletal radiology, or equivalent education and experience in neuroradiology or musculoskeletal radiology. Filler Rebuttal Rep. ¶ 15. In addition, I understand that Plaintiffs contend that a person having ordinary skill in the art will also have substantial experience (*e.g.*, 2 years) designing or studying MRI machines. *Id.*

12. For the purposes of this report and reaching the conclusions herein, and unless stated otherwise, I have applied Plaintiffs' definition of the level of ordinary skill in the art at the time of the invention. My opinions in this report would not change under a reasonable but different definition of the person of ordinary skill in the art.

IV. Summery of Opinions

13. I have been asked to provide my opinion about how one of ordinary skill in the art would understand the "conspicuity of 1.1" (and "an intensity at least 5 times that of the non-neural tissue") phrases in the '360 patent claims, and how and whether one of ordinary skill in the art, if instructed to use the equation proposed by Plaintiffs, would know the methods(s) to use for selecting regions-of-interest ("ROI") for the nerve tissue and non-neural tissue in the calculation of conspicuity in claims 1-35.

14. Plaintiffs have proposed that "conspicuity of 1.1," for purposes of the '360 patent, should be calculated as the mean intensity of nerve tissue in an ROI divided by the mean intensity of non-neural tissue in a different ROI (I will refer to this as $\mathbf{S_n/S_b}$). *See, e.g.*, Filler Rebuttal Rep. ¶¶ 32, 38.

15. As an initial matter, this is a not a standard method of analyzing conspicuity, and the equation itself ($\mathbf{S_n/S_b}$) is unreliable and provides only marginally relevant information about the ability of a person of ordinary skill in the art to distinguish a nerve from other tissue in an image, as more fully explained herein.

16. Even accepting that mathematical definition for "conspicuity of 1.1," however, for the reasons more fully explained herein, it is my opinion that claims 1-35 still fail to reasonably apprise those skilled in the relevant art of the patent applicant's intended scope of the invention, because the underlying method of selecting an ROI for the nerve tissue and non-neural tissue in the calculation of conspicuity in claims 1-35 is subjective and imprecise.

17. There is no industry-standard for selecting ROIs in image quality calculations. Rather, there are many ways of selecting an ROI that are equally reasonable and likely to be used by a person of ordinary skill in the art, and the selection of different ROIs significantly affects

the result of the S_n/S_b calculation. And the '360 patent does not provide any guidance on how an ROI should be chosen to perform the conspicuity calculation in claims 1-35. Thus, persons of ordinary skill in the art could and likely would reach different conclusions about whether a particular image or nerve meets the required "conspicuity of 1.1."

V. Opinions and Analysis

A. Claim Language

18. Claims 1, 3, 7, 11, 12, and 18 in the '360 patent include the phrase "conspicuity of the nerve that is at least 1.1 times that of [the] / [any adjacent] non-neural tissue." Claim 19 includes the phrase "the nerve at an intensity at least 5 times that of the non-neural tissue." As one example, claim 1 includes the limitation:

> processing the output to generate a data set describing the shape and position of said nerve, said data set distinguishing said nerve from non-neural tissue, in the in vivo region to provide a conspicuity of the nerve that is at least 1.1 times that of the non-neural tissue . . . .

'360 patent col. 37 ll. 18-27. My analysis of the phrase "conspicuity of the nerve that is at least 1.1 times" in claims 1, 3, 7, 11, 12, and 18 applies equally to the phrase "the nerve at an intensity at least 5 times" in claim 19.

19. I have been informed by counsel that claims that depend upon these claims incorporate all of the limitations of the claims upon which they depend, so that claims 4-6, and 13 incorporate the "at least 1.1 times that of the non-neural tissue" requirement, and claims 19, 20, 22-26, 28, and 35 incorporate the "at least 1.1 times that of any adjacent non-neural tissue" requirement.

20. I also note that claims 1-35 require that the nerve is "a member of the group consisting of peripheral nerves, cranial nerves numbers three through twelve, and autonomic nerves" and that the Court has construed that phrase to mean "a nerve that is listed in Taber's

Cyclopedic Medical Dictionary (17th ed. 1993) on pages 182, 463 (excluding cranial nerves 1 and 2), 1290, and 1291 and/or that is otherwise not part of the central nervous system." *See, e.g.*, '360 patent col. 37 ll. 6-8; col. 18 l.67-col. 19 l.2; Claim Construction Order at 10.

B. Conspicuity In General

21. In medical imaging, "conspicuity" does not have a standard operational definition, nor is there a single, specific metric known in the art for determining how easily one object can be distinguished from another in an image. Rather, conspicuity is typically understood in the field as a qualitative concept that is generally related to the relative ease of distinguishing one tissue from another in an X-ray, CT scan, MRI, PET, or other medical imaging technique. Thus, to apply the concept of conspicuity to a particular application, such as distinguishing nerve from non-neural tissue in an MRI, one has to define a specific procedure for doing so.

22. Although there are others, including human visual inspection, one way conspicuity can be evaluated is by measurements derived from the image data. While image data is used to produce images for human observation that consist of spatially defined pixels, or voxels, of varying brightness or color, the specific brightness or color of a pixel corresponds to signal measurements recorded by the imaging machine. Measurements of signal properties can be made (within a selected ROI) and compared to other measurements (in other selected ROIs) to try to assess the contrast (or, conspicuity, which I have assumed for purposes of this report to be the same)[1] of a particular structure in the image relative to other structures.

23. In order to determine conspicuity or contrast by measurement, one must specify the calculation to use, because there is no single industry-standard known in the MRI medical

[1] Contrast generally is understood to refer simply to the difference in brightness or grayscale between two objects. Conspicuity, on the other hand, is generally understood to refer to a more complex concept that depends on other factors, such as the size and shape of an object in an image, that affect the ability of an observer to visually distinguish objects in an image.

imaging field. Rather, there are a number of methods and equations known in the art and accepted as standard ways of analyzing conspicuity or contrast, such as: signal-to-noise ("S/N"), contrast-to-noise ("C/N"), full width/half max ("FWHM"), and modulation transfer function ("MTF"). *See, e.g.*, **Ex. D,** Bushberg et al., The Essential Physics of Medical Imaging, 261-262, 270-273, 278-281, 287 (2d Ed. 2002) (discussing S/N, C/N, and MTF); **Ex. E**, R.N. Bryan et al., Introduction to the Science of Medical Imaging, 87-88 (2010) ("Bryan") ("The signal-to-noise ration (SNR, S/N) is a basic measure of image quality . . . ."); *Id.* at 87-88 ([I]n practice, contrast-to-noise (CNR, C/N) is the usual operational unit . . . .").

24. Noise is present in all images and is the signal that is detected by the imaging device, but that does not accurately reflect the sample, *i.e.* the patient. For instance, noise is often perceived as graininess or "salt and pepper" superimposed on the image. *See* Bryan at 87.

25. Because noise obscures the true image signal, it is very important to properly account for, and attempt to reduce, noise in any image analysis. Without doing so, noise can obscure the intrinsic signal differences between two objects or tissues, thereby affecting any conspicuity measurement. Bryan at 87 ("Any received signal containing noise results in ambiguity or uncertainty about the original signal."). Any method of determining image quality or conspicuity that does not take into account noise is flawed.

26. I note that the equation for determining conspicuity proposed by Plaintiffs ($\mathbf{S_n/S_b}$) does not take into account noise. Failing to account for noise is significant because many of the MRI techniques described in the patent and patent claims, such as fat suppression, effectively decrease overall signal-to-noise ratio ("S/N"), which consequently increases the likelihood that noise could obscure the differences in tissue signal intensities and thus the conspicuity measurement. *See* Bushberg at 280-281, 287 ("As objects get smaller and lower in

contrast, their SNR is reduced and they become harder to see on the image."); Bryan at 87 ("While contrast is important, its practical merit lies in relationship to noise. . . [T]he intrinsic contrast between the objects is confounded by noise. Noise always decreases the relative contrast between two objects. Hence, in practice, contrast-to-noise (CNR, C/N) is the usual operational unit . . . .").

27. For example, as explained in Bushberg, it is virtually impossible to determine the boundaries of structures in a relatively noisy image, and one could not therefore accurately assess the conspicuity of structures in such an image. *See* Bushberg at 280-81 ("Better contrast resolution implies that more subtle objects can be routinely seen on the image. Contrast resolution is very much related to the SNR . . . ."); Fig. 10-30.

C. "Conspicuity" in the '360 Patent

28. Plaintiffs propose that the '360 patent defines $\mathbf{S_n}$ and $\mathbf{S_b}$ as the average/mean signal intensity of the pixels within each "region-of-interest" ("ROI"). Filler Rebuttal Rep. ¶¶ 32, 38. For the purposes of this report, I have adopted Plaintiffs' use of the average/mean to calculate signal intensity.

i. Regions of Interest ("ROI") in General

29. To quantify conspicuity of a nerve based on signal measurements (whether according to Plaintiffs' proposed $\mathbf{S_n/S_b}$ ratio or by another more common method), one must take two measurements from the same image, one from the neural tissue and the other from a region of non-neural tissue. *See* Filler Rebuttal Rep. at 17 n.5, Ex. A. The part of an image from which a particular measurement is made is called a region-of-interest ("ROI").

30. Any measurement of an ROI is highly dependent upon the composition of pixels included in the ROI. How the ROI is selected and defined therefore substantially impacts the

average/mean signal intensity, thus affecting the ultimate conspicuity measurement. *See* **Ex. F,** N.C. Krak et al., *Effects of ROI Definition and Reconstruction Method on Quantitative Outcome and Applicability in a Response Monitoring Trial*, 32 Eur. J. Nuclear Med. & Molecular Imaging 294 (2005) ("Krak") ("*Conclusion:* The method of ROI definition has a direct influence on quantitative outcome."); *id.* at 294-95 ("It is clear that the method of ROI definition will affect quantitative measurements of tracer uptake.");[2] **Ex. G,** Y. Ozsunar et al., *MRI Measurements of Water Diffusion: Impact of Region of Interest Selection on Ischemic Quantification*, 51 Eur. J. Radiology 195, 199 (2004) ("Ozsunar") ("Our findings extend earlier studies by showing that ADC quantification is significantly affected by the method of ROI measurement."); Ozsunar at 197 ("ROI selection significantly affected ADC measurement both in relative ($P < 0.01$) and absolute values ($P < 0.001$)."); *see also* ¶¶ 41-58.

31. In medical imaging, there is no recognized standard for selecting an ROI. *E.g.*, **Ex. H,** S. Mussurakis, *Dynamic MR Imaging of the Breast Combined with Analysis of Contrast Agent Kinetics in the Differentiation of Primary Breast Tumors*, 52 Clinical Radiology 516, 524 (1997) ("Mussurakis") ("[A] standardized method of ROI selection and analysis of dynamic breast MR data is yet to be established."); Bushberg, at 700 ("Some programs use the same ROI around the left ventricle for both images, whereas, in other programs, the ROI is drawn separately in each image to better fit the varying shape of the ventricle."); Ozsunar at 199 ("Despite many ROI options, there is no consensus about the best method, the advantages and disadvantages and how one can compare the results obtained by using variable ROI techniques."); **Ex. I,** R. Boellaard et al., *Effects of Noise, Image Resolution, and ROI Definition*

[2] Some of the articles cited herein employ medical imaging techniques other than MRI, such as PET. The points for which I have cited these articles (*e.g.*, regarding selection and measurement of ROIs) apply equally to MR imaging.

on the Accuracy of Standard Uptake Values: A Simulation Study, 45 J. Nuclear Med. 1519, 1520 (2004) ("Boellaard") (listing "various types of ROIs that are in regular use," including "maximum pixel value only" and "15 x 15 mm square ROI centered on the location of maximum pixel value"). In fact, the '360 patent acknowledges that there are various options for selecting ROIs:

> [O]ne or more regions of interest (ROI) within the image can be identified. Each ROI may be a single pixel or voxel, or a larger region. ROI selection can be performed manually using, for example, a keyboard or mouse to move a cursor over the ROI on the displayed image. Alternatively, ROI selection may be accomplished automatically via a sequential selection of all pixels or via an external input regarding a particular region from, for example, diagnostic system 24.

'360 patent col. 14 ll. 53-63. *See also* Bushberg, at 699 ("[An ROI] may be drawn manually or it may be drawn automatically by the computer.").

32. Thus, for the type of conspicuity measurement here, it is critical to specifically define how to select the ROIs used in the measurements. *See* Bryan at 87-88 ("The calculation of CNR requires the explicit definition of objects, at least two in this case."). Without doing so, selection of an ROI would depend upon the subjective choice of the operator. *See* Ozsunar at 199 ("ROI positioning and selection should be accurate, reproducible, objective, independent of to investigator bias, equally applicable in both clinical and research settings, time efficient and cost effective."); Mussurakis at 524 ("Limitations of [the ROI] approach include the fact that only subjectively selected regions are examined and that pixel measurements of the chosen regions are averaged.").

33. Indeed, this problem is widely recognized in the medical imaging field, and as a result, when an application calls for evaluating image quality or characteristics based on an ROI, the precise parameters and protocol for selecting the ROI are specified. *See, e.g.*, Ozsunar at 196 ("a 2 x 2 pixel ROI was placed in the geographic center of the lesion and along the lateral and

medial rim of the lesion" for MR imaging); **Ex. J,** B.J. Soher, *et al.*, *Magnetic Resonance Perfusion Imaging in Acute Middle Cerebral Artery Stroke: Comparison of Blood Volume and Bolus Peak Arrival Time*, J. of Stroke and Cerebrovascular Diseases, Vol. 7, No. 1, 17, at 19 (Jan./Feb. 1998) ("Soher") (performing analysis on "5 x 5-pixel regions of interest (ROI)" for four specific areas of an MR image); Boellaard at 1520 (describing specific parameters and methodologies for selecting various ROIs); Krak at 295; **Ex. K,** G. D. Mitsis, *Regions of Interest Analysis in Pharmacological fMRI: How Do the Definition Criteria Influence the Inferred Result?*, 40 NeuroImage 121, 121-122 (2008) ("Mitsis") (examining "the choices made in region of interest analysis of a human pain pharmacological fMRI experiment, by systematically assessing their influence on the inferred results," and defining "individual ROIs . . . based on anatomical landmarks"); **Ex. L,** M. Brett, *MarsBaR Documentation: Release 0.42*, 13-19 (2010) ("Brett") (describing different methods of ROI selection used in ROI analysis program).

34. For instance, Krak specifically identified and used "a wide variety of methods for ROI definition," including:

> manual placement of ROIs covering the whole tumour using either average counts or maximum pixel value . . ., placement of ROIs with fixed dimensions around the "hottest" area within a tumour . . ., and the use of isocount countour ROIs with thresholds varying from 50% to 95% of the maximum pixel value.

Id. Krak then more specifically defined how to select the ROIs for each method, such as: "circular 15-mm-diameter ROIs were drawn semi-automatically over the area of maximum FDG uptake in a lesion . . . ." *Id.* at 295; *see also* Boellard at 1520 (specifying ROI methods including "3D isocontour at 50% of maximum pixel value within tumor (ROI^{50})," "maximum pixel value only," and "15 x 15 mm square ROI centered on the location of maximum pixel value (ROI^{15x15})"). Krak concluded that "[t]he method of ROI definition has a direct influence on

quantitative outcome." Krak at 294; *see* Ozsunar at 197-99 ("the method of ROI measurement" significantly affects MRI measurements).

35. Importantly, however, nothing in the '360 patent itself or the prosecution history indicates the precise method for selecting the appropriate ROI for the conspicuity calculation required by the claims. Rather, the '360 patent simply leaves open the possibility of using any method of selecting an ROI, of which there are many. *See, e.g.*, Brett at 13-19 (2010) (describing different methods of ROI selection used in ROI analysis program); Mitsis, at 121-122 (cataloging various methods of anatomical and functional ROI selection methods); Krak, at 299 (identifying four commonly-used methods of ROI selection for quantitative analysis, such as "manual, fixed dimensions, threshold based and maximum pixel value"); Boellaard, at 1520 (identifying five commonly-used methods of ROI selection for quantitative analysis); Ozsunar at 195 ("This variation may arise to some extent from using different region of interest (ROI) measurement techniques."). As a result, as explained below in ¶¶ 36-45, the conspicuity calculation proposed by Plaintiffs depends on factors and choices that are left to the subjective choice of the person of ordinary skill in the art, with no guidance from the '360 patent.

36. First, manually selecting the appropriate ROI is dependent upon the observer's subjective ability to visually distinguish the boundary between two tissues, *i.e.*, the neural tissue and the non-neural tissue. *See* Mussurakis at 524 ("Observer variability is inherent in the subjective region of interest drawing."). The observer would manually outline or place a geometric-shaped ROI over what he or she perceives as the correct tissue. This is usually based on a combination of prior knowledge of what a particular structure should look like and some clues from the image itself as to where the structure might be. If the observer cannot accurately do so, then the observer will not know where to place the ROI and they will not know whether a

selected ROI includes only neural tissue. The poorer the image clues (*e.g.*, the lower the contrast, or the higher the noise), the harder the task and the more important prior knowledge becomes. Yet, the method proposed by Plaintiffs does not take into account factors such as noise, factors that can significantly compromise any observer's ability to distinguish different tissues.

37. As demonstrated in the **Exhibit C**[3] of this report, the proposed MRI methodology of the '360 patent (as asserted by Plaintiffs in this case) does not appear to yield images with signal intensity clues sufficient to identify nerves based on signal intensity alone. One of ordinary skill would not likely have sufficient prior knowledge (for a particular patient) of where the pertinent nerves are located or what the nerves look like for the vast majority of peripheral, autonomic, or cranial nerves (which are the nerves claimed in claims 1-35). While a general radiologist would have some limited knowledge of where nerves might be, and while a subspecialty-trained neuroradiologist or musculoskeletal radiologist might have more detailed knowledge of the expected anatomy of major nerves to match with the signal intensity clues contained in the image, few practitioners would have detailed knowledge of smaller peripheral nerves. And no practitioner would have robust knowledge of where a nerve might be when located in an unexpected or abnormal position (which is often the case when patients require an MRI).

[3] The Figures and Tables in **Exhibit C** of this report were created from the same DICOM data Dr. Filler used in Exhibit A to the Filler Rebuttal Report. **Exhibit C**, Figure 1 (and accompanying table) was created from the data corresponding to Figure 4 in Ex. A of the Filler Rebuttal Report. **Exhibit C**, Figure 2 (and accompanying table) was created from the data corresponding to Figure 2 in Ex. A of the Filler Rebuttal Report. **Exhibit C**, Figures 3, 5-11 (and accompanying tables) were created from the data corresponding to Figure 3 in Ex. A of the Filler Rebuttal Report. **Exhibit C**, Figure 4 (and accompanying table) was created from the data corresponding to Figure 8 in Ex. A of the Filler Rebuttal Report.

38. Second, claims 1 through 35 in the '360 patent claim methods of making images in which peripheral, autonomic, and certain cranial nerves have a signal intensity that is only at least 10% greater than other non-neural tissues. However, an observer's ability to subjectively discriminate between small changes in degrees of brightness is limited, and is also dependent on the complexity and shape of the structure. It is entirely possible that an image could inherently have a $\mathbf{S_n/S_b}$ of 1.1, but that the nerves cannot be reliably distinguished from other tissues (such that the actual inherent $\mathbf{S_n/S_b}$ cannot actually be determined). In those cases, the relevant ROIs could not be selected because the observer would not be able to determine what is nerve tissue and what is non-neural tissue. While one of ordinary skill in the art may be able to make an educated guess about the general location of neural tissue, simply identifying the nerve does not necessarily mean that the image allows the observer to accurately distinguish between tissue boundaries so that ROIs can be selected for both neural and non-neural tissue, nor does it tell the observer which pixels (*i.e.*, size, shape, and position) to include.

39. Third, factors (including, for instance, size, shape, and position of the ROI) can significantly change the resulting signal measurements that are input to the $\mathbf{S_n/S_b}$ equation. As demonstrated below with exemplary measurements, *see* ¶¶ 41-57 and **Exhibit C**, the result of the signal measurement depends significantly on the size, shape, and position of the ROI. *See, e.g.*, Krak at 295 (noting statistically significant differences between measured values of parameter dependent on the ROI selected); Ozsunar at 199 (quantitative results "significantly affected by the method of ROI measurement"). But the '360 patent does not specify how to set the size, shape, or position of the ROIs. And there is no accepted standard for one of ordinary skill in the art to select the size, shape, or position of an ROI, which was true at the time of the invention and remains true today. *See* ¶¶ 30-34. Rather, MRI scientists precisely define protocols for

selecting ROIs, for each particular application or study, to avoid the very problem present here, where all these choices are left to the subjectivity of the operator. *See* ¶¶ 33-34. Otherwise, a person of ordinary skill in the art would reasonably and likely select different ROIs and therefore calculate different conspicuity values.

40. Fourth, while one can alternatively use an ROI selection algorithm (commonly known as "segmentation algorithms") as the '360 patent acknowledges, the patent fails to provide any specificity as to which algorithm to use. '360 patent col. 14 ll. 53-63. To the extent one chooses to use a segmentation algorithm, there are many known segmentation algorithms in the art and there is no industry standard. *See, e.g.*, **Ex. M,** D. L. Pham et al., *Current Methods in Medical Image Segmentation*, 2 Annu. Rev. Biomed. Eng. 315 (2000) (describing eight categories of segmentation algorithm approaches); **Ex. N,** M. Jolly, *Automatic Recovery of the Left Ventricular Blood Pool in Cardiac Cine MR Images*, MICCAI, Part I, LNCS 5241, 110 (2008) (describing segmentation algorithm for MRI of left ventricle); **Ex. O,** K. C. Tam et al., *Exact (Spiral + Circles) Scan Region-of-Interest Cone Beam Reconstruction via Backprojection*, 19(5) IEEE Transactions on Medical Imaging 376, (May 2000) (describing segmentation algorithm for reconstructed ROI of oblong object via backprojection in X-ray); **Ex. P,** E. Klotz et al., *Automated Definition and Evaluation of Anatomical ROI's for Bone Mineral Determination by QCT*, 8(4) IEEE Transactions on Medial Imaging 371 (Dec. 1989) (describing segmentation algorithm for automatically locating spinal canal for QCT)**.** In my research, I have developed segmentation algorithms, and in my experience each algorithm would result in the selection of a different ROI and therefore different mean signal intensity for a particular tissue. To my knowledge there is no algorithm that can reliably define the boundary of most of the nerves that are in the categories of nerves listed in the claims.

ii. Conspicuity Analysis and Exemplary Calculations

41. To demonstrate the subjectivity of selecting an ROI, and how that subjectivity impacts the conspicuity calculations, I have performed various calculations on the image data sets ("DICOM data") used in the Filler Rebuttal Report, which Dr. Filler contends are "infringing" images (which I understand to mean that Plaintiffs contend those images were made using the methods claimed in the '360 patent). *E.g.*, Filler Rebuttal Rep. ¶ 48. These calculations are attached as **Exhibit C.**

42. As demonstrated below, whether the "conspicuity" limitation of claims 1-35 would be met is impacted by how the ROI is selected and is highly subjective, since there is not a universally agreed upon method in the field of the invention for selecting ROIs.

43. First, I note that, in Exhibit A to the Filler Rebuttal Report, Dr. Filler made many choices about which nerves to identify and how to draw ROIs within them, without explaining his reasons for doing so, which highlights the arbitrary and subjective nature of determining whether the "conspicuity" limitation is met. For example, Dr. Filler has chosen to measure the conspicuity of the largest peripheral nerves with the most identifiable physiology, such as the brachial plexus, which are (not surprisingly) the easiest nerves to identify and measure. *See, e.g.*, Filler Rebuttal Rep. Ex. A, Figs. 2 & 4. From my review, however, none of the images in Exhibit A to the Filler Rebuttal Report identify—much less with the claimed 1.1 conspicuity—the smaller peripheral nerves, which undoubtedly makes the task of selecting an appropriate neural ROI for a conspicuity measurement of these nerves exceedingly difficult and subjective. Further, even for the nerves Dr. Filler identified as meeting the 1.1 conspicuity requirement, there are ROIs that a person of ordinary skill in the art could reasonably select that lead to conspicuity calculations of less than 1.1. *See* **Ex. C**, Figs. 1-6 & Tables 1-6. There is no basis in the patent or the knowledge of a person of ordinary skill in the art to select the ROIs Dr. Filler

used instead of other ROIs that show a conspicuity of less than 1.1 for these nerves. In addition, Dr. Filler has chosen to use ROIs of different size and shape, but provides no reasons for the arbitrary choices he has made. *See* Filler Rebuttal Rep., Ex. A, Figs. 2-4 (showing ROIs of different sizes and shapes). Moreover, Dr. Filler has chosen, quite arbitrarily, various types and locations of non-neural tissue. *Id.*

44. Second, the '360 patent fails to specify how much or how many of the neural/non-neural tissues must be used in the conspicuity calculation. Yet, the conspicuity calculation, and the ability to perform one, is greatly impacted by these variables. For example:

a. To the extent that the identified nerve must be 10% brighter than ***all of the non-neural tissue in the image***, the images that Plaintiffs contend were produced from the patented methodology fail to meet this standard, as demonstrated in **Exhibit C**. *See, e.g.*, **Ex. C.**, Fig. 3 & Table 3 (showing that non-neural ROIs 2-4 and 14 are at least 10% brighter than any neural ROI). In other words, the neural tissue is not the brightest tissue in the images. Likewise, to the extent that ***all of the nerves must be 10% brighter*** than only some non-neural tissue, the images that Plaintiffs contend were produced from the patented methodology fail to meet this standard again, because some nerves are not 10% brighter. *See, e.g.*, *id.* In other words, there are some nerves in the images that are relatively dark compared to the surrounding tissue.

b. On the other hand, if a nerve need only be 10% brighter ***than a single non-neural tissue in the entire image***, or if only ***one nerve*** needs to be 10% brighter than ***some non-neural tissue***, a potential infringer would be required to search an entire image for a very specific set of ROIs, which may not exist. This problem is further exacerbated by the fact that, as explained above, *see* ¶¶ 36-37, even a person with superior skill in the art may not be able to identify, and distinguish between, all neural/non-neural tissue in an image. Although the

brachial plexus or larger spinal nerves can usually be identified in an MR image simply because of their size, shape, and position, that is not the case for many peripheral nerves, autonomic nerves, and cranial nerves 3 through 12. As such, this requirement becomes unworkable for images of anatomic regions that do not include readily identifiable nerves like the brachial plexus, and one could not accurately determine whether they have met the "conspicuity" limitation, nor understand the scope of the claims.

45. As a practical matter, consequently, in virtually any image (regardless of whether it was made by the supposedly patented method), a person of ordinary skill in the art could reasonably choose ROIs for nerve and non-neural tissue that show "conspicuity of 1.1" and also ROIs showing a conspicuity of less than 1.1. This is especially true here, since neither the patent nor the knowledge of a person of ordinary skill in the art provides guidance as to which or how many pixels should be included in the ROI. In fact, the '360 patent explicitly allows "[e]ach ROI [to] be a single pixel or voxel." '360 patent col. 14 ll. 56. In most tissues, however, there will be some relatively light pixels, some relatively dark pixels, and a relatively broad spectrum of pixels in between. Thus, a single pixel ROI, as envisioned by the '360 patent, can lead to conspicuity values that vary widely above and below 1.1. For example, the histogram below, which represents the single-pixel intensities in the estimated-freehand ROI of the entire C7 Spinal Nerve in **Exhibit C**, Figure 11, demonstrates the wide-ranging pixel intensities in the nerve, any of which could reasonably be selected as an ROI according to the '360 patent. The pixel intensities for the C7 Spinal Nerve appear to vary from 49 to 113. Although the mean pixel intensity is 80, the standard deviation is more than 14, suggesting a wide range of pixel values within the nerve, which is reflective of intrinsic tissue signal intensity variability and image

noise. The same sort of variation will occur in the non-neural tissue, further compounding the problem.

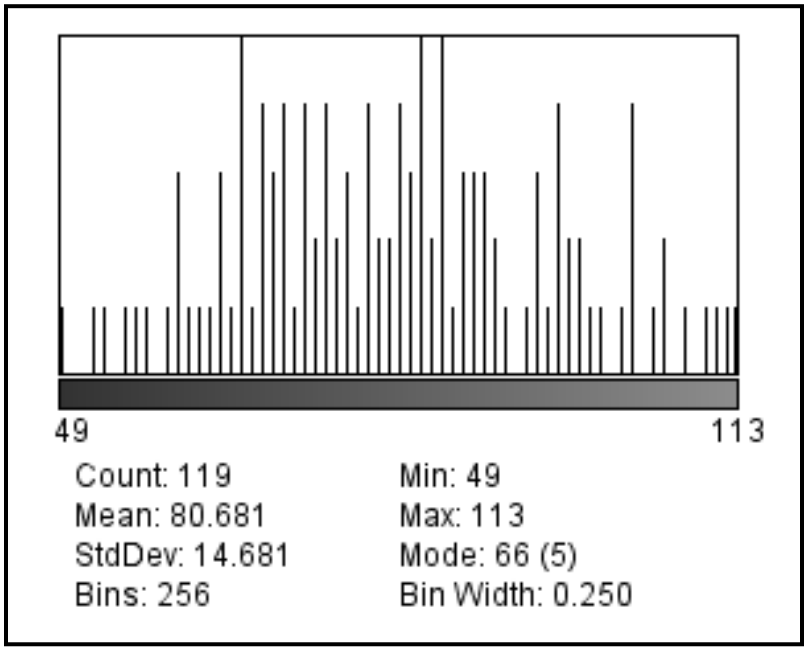


Exhibit C, Table 11.[4]

a) Average Signal Intensities Based on Different ROI Selections in the Neural Tissue

46. Claims 1, 3, 7, 11, and 12 require "a conspicuity of the nerve that is at least 1.1 times that of the non-neural tissue." As an initial matter and as noted above, *see* ¶¶ 44-45, neither the claims nor the '360 patent provide sufficient guidance about what the claimed "nerve" is, or how to select an ROI within it, for purpose of the neural ROI. I recognize that claim 18 (but not claims 1 through 17) suggests including the "epinurium and perinerium" as part of the "nerve," but the '360 patent otherwise provides no guidance about selecting the "nerve," or which parts of a "nerve" to include. Thus, for example, one of skill in the art could reasonably choose to include the nerve sheath or fat, or one could choose to select an entire nerve

[4] Figure 11 and Table 11 in Exhibit C were created using NIH's ImageJ, version 1.44.

bundle. On the other hand, one of skill in the art could chose to select only the nerve axon or an individual fascicle. The patent provides no guidance as to which of these tissues should be included in the calculation of conspicuity. Yet each of these components of a "nerve" will have different signal intensities, and therefore the mean intensity of the "nerve" will be affected by which of these components is included in the nerve.

47. As demonstrated in **Exhibit C**,[5] Figure 7 and Table 7 (which were created from the same image data Dr. Filler used for Ex. A, Fig. 3 of his report), the mean signal intensity varies greatly depending on the size, shape, and placement of the ROI for the neural tissue—specifically, a difference in signal intensity of 40.3 ***resulting in a 54% variation*** based solely on the size, shape and position of the ROI within the nerve tissue. That level of variation will proportionately affect the conspicuity calculation.

ROI of Nerve Tissue	**Mean Signal Intensity**
ROI #1	98.3
ROI #2	73.9
ROI #3	114.2
ROI #4	94.3
ROI #5	76.0

Exhibit C, Table 7.

48. Even when only moving the position of the ROI along the nerve (keeping the size and shape relatively constant), significant variations in mean signal intensity result, as demonstrated by **Exhibit C**, Figure 8 and Table 8 (which were created from the same image data Dr. Filler used for Ex. A, Fig. 3 of his report). Specifically, there is a difference in signal intensity of 40.2 ***resulting in approximately a 60% variation*** solely from moving the position of

[5] Figures 1-10 in Exhibit C were created using the Osirix Imaging Software.

the ROI within the nerve. That level of variation will proportionately affect the conspicuity calculation.

ROI of Nerve Tissue	Mean Signal Intensity
ROI #1	77.0
ROI #2	92.1
ROI #3	103.4
ROI #4	89.0
ROI #5	70.5
ROI #6	112.5
ROI #7	91.8
ROI #8	78.0
ROI #9	80.5
ROI #10	72.0

Exhibit C, Table 8.

49. Accordingly, it is my opinion that the ROI selection of the neural tissue is a subjective inquiry, which will have a significant impact on the conspicuity measurement required by claims 1-35. Calculation or measurement to determine whether an image shows a "nerve at an intensity at least 5 times that of the non-neural tissue" would be subject to the same subjectivity and variability.

b) Average Signal Intensities Based on Different ROI Selections in the Non-Neural Tissue

50. Claims 1, 3, 7, 11, and 12 require "a conspicuity of the nerve that is at least 1.1 times that of the non-neural tissue." As mentioned in ¶¶ 44-45, nothing in the claims or the '360 patent discloses how to select the "non-neural" tissue.

51. As demonstrated in **Exhibit C**, Figure 9 and Table 9 (which were created from the same image data Dr. Filler used for Ex. A, Fig. 3 of his report), the mean signal intensity varies greatly depending on the size, shape, and placement of the ROI, as well as the type of non-neural tissue selected (*e.g.*, bone, muscle, etc.)—specifically, a difference in signal intensity of

44.5 ***resulting in a 79% variation.*** That level of variation will proportionately affect the conspicuity calculation. Yet, the '360 patent provides no guidance on what tissue to select.

ROI of Non-Neural Tissue	**Mean Signal Intensity**
ROI #1	82.0
ROI #2	66.5
ROI #3	56.0
ROI #4	86.3
ROI #5	65.6
ROI #6	61.1
ROI #7	78.5
ROI #8	100.5

Exhibit C, Table 9.

52. Claim 18 recites "a conspicuity of the nerve that is at least 1.1 times that of ***any adjacent*** non-neural tissue." No matter whether "any adjacent non-neural tissue" must include all of the "adjacent non-neural tissue" or, instead, whether "any adjacent non-neural tissue" only requires including in the ROI a portion of the "adjacent non-neural tissue" (for example a two pixel/voxel border around the neural tissue), the mean signal intensity of the "adjacent non-neural tissue" varies significantly depending on the size, shape, and placement of the ROI. **Exhibit C**, Figure 10 and Table 10 (which were created from the same image data Dr. Filler used for Ex. A, Fig. 3 of his report), demonstrate a difference in signal intensity of "any adjacent" non-neural tissue of 37.6 ***resulting in approximately a 36% variation***. *See also* Fig. 5 & Table 5 (showing that the nerve has a conspicuity of less than 1.1 as compared to the adjacent non-neural tissue). That level of variation will proportionately affect the conspicuity calculation.

ROI of "Any Adjacent" Non-Neural Tissue	Mean Signal Intensity
ROI #1	143.0
ROI #2	114.6
ROI #3	105.4
ROI #4	123.8

Exhibit C, Table 10.

53. Accordingly, it is my opinion that the ROI selection of the non-neural tissue/adjacent non-neural tissue is a subjective inquiry, which will have a substantial impact on the conspicuity measurement. Calculation or measurement to determine whether an image shows a "nerve at an intensity at least 5 times that of the non-neural tissue" would be subject to the same subjectivity and variability.

c) Conspicuity Calculations Based on Different ROIs

54. As demonstrated in **Exhibit C**, Figures 1-4 and Tables 1-4, the final conspicuity calculation is highly impacted by the ROI selection, and, as discussed above in ¶¶ 28-53, the selection of the ROI for purposes of the '360 patent is left to the subjective choice of the operator. Even the peripheral nerves identified by Dr. Filler as having a conspicuity of greater than 1.1 in the exhibits to his expert report have a conspicuity of ***less than 1.1*** depending on the selection of ROI. *See e.g.*, **Ex. C**, Figs. 1-4 & Tables 1-4. For example, all of the **bolded** conspicuity measurements below in **Exhibit C**, Table 3, show peripheral neural tissue with a ***conspicuity of less than 1.1*** as compared to non-neural tissue, even though these measurements were created from the same image data Dr. Filler used for Ex. A, Fig. 3 of his report to show nerves with a ***conspicuity of greater than 1.1***. Based on what is described in the patent and the knowledge of a person of ordinary skill in the art, the ROIs in **Exhibit C** are equally reasonable choices compared to the ROIs selected by Dr. Filler, and yet the conspicuity values vary widely (above and below 1.1) for different selections of ROIs.

Conspicuity Calculations from Measurements in Figure 3								
			ROI # (Nerve Tissue)					
			#5	#6	#7	#8	#12	#13
		Intensity	99.7	78.7	88.1	61.4	74.9	109.4
ROI # (Non-Neural Tissue)	#1	94.3	**1.06**	**0.83**	**0.93**	**0.65**	**0.79**	1.16
	#2	168.2	**0.59**	**0.47**	**0.52**	**0.37**	**0.45**	**0.65**
	#3	131.8	**0.76**	**0.60**	**0.67**	**0.47**	**0.57**	**0.83**
	#4	136.1	**0.73**	**0.58**	**0.65**	**0.45**	**0.55**	**0.80**
	#9	114.6	**0.87**	**0.69**	**0.77**	**0.54**	**0.65**	**0.95**
	#10	85.1	1.17	**0.92**	**1.04**	**0.72**	**0.88**	1.29
	#11	92.1	**1.08**	**0.85**	**0.96**	**0.67**	**0.81**	1.19
	#14	217.1	**0.46**	**0.36**	**0.41**	**0.28**	**0.35**	**0.50**
	#15	77.1	1.29	**1.02**	1.14	**0.80**	**0.97**	1.42
	#16	56.6	1.76	1.39	1.56	**1.08**	1.32	1.93
	#17	100.3	**0.99**	**0.78**	**0.88**	**0.61**	**0.75**	**1.09**

Exhibit C, Fig. 3 and Table 3.

55. In addition, several ROIs in Figure 3 and Table 3 (which were created from the same image data Dr. Filler used for Ex. A, Fig. 3 of his report), such as ROIs 2-4 and 14, are non-neural tissue (bone or glands), but are the brightest, most "conspicuous" tissues in the image. In fact, none of the neural tissue in Figure 3 is brighter than the non-neural tissue in ROIs 2-4 and 14. Similarly, Dr. Filler showed nerves with a conspicuity of greater than 1.1 in Figure 4 of his report, but with that same data **Exhibit C**, Figure 1 and Table 1, show non-neural ROIs that are brighter than neural ROIs, including ROIs placed on the brachial plexus. *See* **Ex. C**, Fig. 1 & Table 1; *see also id.* Fig. 2 & Table 2 (showing nerve ROIs, including the brachial plexus, with a conspicuity of less than 1.1 compared certain non-neural ROIs).

56. **Exhibit C**, Figure 4 and Table 4, (which were created from the same image data Dr. Filler used for Ex. A, Fig. 4 of his report), is yet another example how the conspicuity calculation greatly depends on the subjective selection of the ROIs. Indeed, although Dr. Filler found ROIs with a conspicuity of greater than 1.1 on this same data, based on the selection of

ROIs in **Exhibit C,** Figure 4 and Table 4, no nerve has a conspicuity of greater than 1.1 as compared to the non-neural tissue. *See* **Ex. C**, Fig. 4 & Table 4. Based on the text and figures in the '360 patent and the knowledge of a person of ordinary skill in the art, these ROIs are equally reasonable choices compared to the ROIs selected by Dr. Filler.

Conspicuity Calculations from Measurements in Figure 6				
			ROI # (Nerve Tissue)	
			#4	#5
		Intensity	161.9	264.8
ROI # (Non-Neural Tissue)	#1	259.5	0.62	1.02
	#2	284.7	0.57	0.93
	#3	284.5	0.57	0.93
	#6	333.7	0.49	0.79
	#7	284.7	0.57	0.93
	#8	263.2	0.62	1.01
	#9	345.4	0.47	0.77
	#10	737.0	0.22	0.36

Exhibit C, Table 4.[6]

57. Likewise, in **Exhibit C**, Figure 5 and Table 5 (which were created from the same image data Dr. Filler used for Ex. A, Fig. 3 of his report), the nerve has a conspicuity of ***less than 1.1 as compared to the "adjacent non-neural tissue."*** In Figure 5, the spinal nerve is in fact darker than the surrounding non-neural tissue, which consists of fat and vessels that appears as bright white and shows a conspicuity of as low as 0.775. *See* **Ex. C**, Fig. 5 & Table 5.

58. In the Filler Rebuttal Report Exhibit A, Figure 3, Dr. Filler opines that the C7 Spinal Nerve on the left side of the image meets the conspicuity limitation. Filler Rebuttal Rep., Ex. A, Fig. 3. As shown in **Exhibit C**, Figure 6 and Table 6, however, the conspicuity of the same C7 Spinal Nerve is less than 1.1 times that of the adjacent non-neural tissue depending on

[6] Based on Figure 4 alone, it is not absolutely clear whether ROI #6 includes only non-neural tissue, or whether it contains some neural tissue as well.

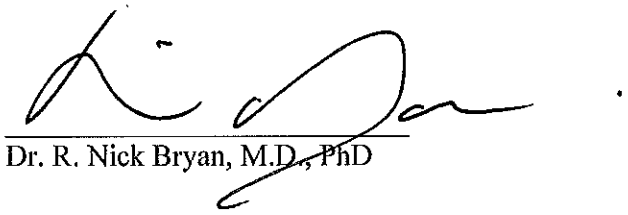
the selection of the ROIs (or at least so close to exactly 1.1 that determining whether the claim limitation is satisfied would change based on minute changes to the ROIs).

Conspicuity Calculations from Measurements in Figure 6		
Mean Signal Intensity	ROI #3 (Nerve): 66.1	ROI #4 (Nerve): 68.3
ROI #1 (Non-Neural): 65.4	**1.01**	**1.04**
ROI #2 (Non-Neural): 67.8	**0.97**	**1.01**

Exhibit C, Table 6.

I declare (or certify, verify, or state) under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on: July 22, 2011



Dr. R. Nick Bryan, M.D., PhD